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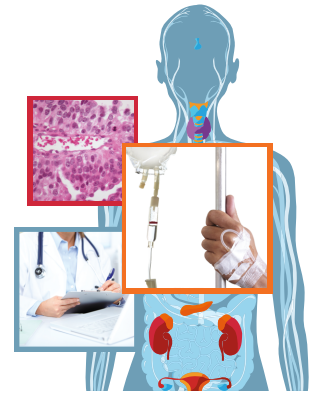

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Novel therapies against aggressive differentiated thyroid carcinomas

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The incidence of thyroid cancer (TC) is increasing. Although the majority of these cancers have a good prognosis, 10% of these will develop local recurrence and/or distant metastases. Conventional cytotoxic chemotherapy has been largely replaced by molecular-target therapies, but it can still have a role. Two tyrosine kinase inhibitors have been approved for the treatment of advanced differentiated TC. They significantly improve progression-free survival, but at the cost of frequent and potentially serious adverse effects. At the moment, there are multiple clinical trials with other tyrosine kinase inhibitors and other drugs. We present a review of the current standard of care and what is up to come in the treatment of advanced TC.

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Thyroid cancer (TC) is a worldwide growing health issue since its incidence is increasing faster than any other neoplasia [1–3]. This fact seems to be related to a greater use of imaging techniques (mainly neck ultrasound) leading to an early diagnosis and treatment of TC. This increase in incidence has no impact in disease-related mortality, which remains at approximately 3% [1,4]. Despite low overall mortality, clinicians face a heterogeneous disease with highly variable survival depending on the tumor histotype and differentiation. Survival rates of TC can be as high as 95% after 35 years of diagnosis for papillary thyroid carcinoma (PTC) or as low as less than 10% at 6 months for anaplastic TC (ATC) [5,6].

Most commonly, TC arises from follicular cells (>90%) that can give rise to differentiated TC (DTC), either PTC or follicular TC (FTC) and, less commonly, poorly differentiated TC (PDTC) and ATC [7]. Other histotypes are derived from the parafollicular cells that give rise to medullary TC (MTC) and very uncommonly from stromal cells (sarcoma) and lymphoid tissue (lymphoma) [7–9].

The treatment of DTC relies on the fact that the tumors derived from follicular cells are able to iodine organification and secrete thyroglobulin under stimulation by thyrotropin-stimulating hormone. Iodine retention is promoted by the sodium–iodine symporter, which is expressed in most DTCs [10]. Due to this fact, the majority of DTCs are treatable with surgery and radioiodine (RAI) [11].

A minority (around 10%), however, will become dedifferentiated, losing the ability to uptake iodine, leading to a rapid progression of local recurrence and/or distant metastases. These patients have a poor prognosis and shorter survival [12]. RAI-refractory TC (RAIRTC) can generally be defined as a tumor that does not concentrate or loses the ability to uptake RAI overtime; RAI concentrates in some lesions but not in others; disease progresses despite RAI uptake [11]. Another definition, although not consensual, is when patients reach >600 mCi of RAI therapy since the maximum benefit is usually obtained at lower activities [13].

RAIRTC can be treated in several ways. Some patients remain asymptomatic with a stable or minimally progressive disease for years and can be kept under surveillance. Patients with symptomatic lesions (namely, cervical and bone

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lesions) can be treated with local therapies such as radiotherapy or, more recently, radiofrequency ablation therapy in focal metastatic lesions [11].

The objective of this article is to focus in the recent therapies against aggressive, advanced DTC.

Methods

A medical literature search was conducted between April and June 2017. Resources included MEDLINE via PubMed, EMBASE, Clinical Trials Databases, Cochrane Library and selected references cited in other articles. We used the controlled language of each database.

The search query was (Novel OR Recent OR Advances OR New) AND (therapy OR treatment) AND aggressive AND (thyroid carcinomas OR thyroid neoplasms). The combination of these keywords was used to search the electronic databases. The included studies must have recent advances in pharmacological therapies for advanced TC, been published in the last 7 years and be written in English. Relevant studies mentioned in articles included in our search were also considered (even if older than 7 years only because of their relevance in a purpose of giving a context).

We excluded studies published more than 7 years ago, those published in a language other than English, case reports and articles focusing exclusively PDTC, ATC or MTC.

After performing the initial literature searches, each study title and abstract was screened for eligibility. Full text of all potentially relevant studies was subsequently retrieved and further examined for eligibility. 59 articles were included in this review.

Conventional cytotoxic chemotherapy

For multiple and progressive metastatic lesions with a high-tumor burden, some cytotoxic therapies have been applied [14]. Historically, adriamycin alone or in combination has been the most-common cytotoxic drug used. A retrospective study from 2008 with adriamycin alone showed only a modest efficacy with one patient achieving a partial response out of 22 patients [15]. Another retrospective study from 2013 with adriamycin plus cisplatin or cyclophosphamide showed a response rate of 20% [16].

Other studies with nonadriamycin-based regimens have shown more consistent benefit. One from 2002 using carboplatin plus epirubicin showed a response rate of 43% in 14 RAIRTC patients [17] and another from 2012 with the gemcitabine plus oxaliplatin regimen showed an overall response of 57%. Most patients had pulmonary and lymph node metastases [14,18]. These cytotoxic protocols can be useful and need further investigation. A Phase II study evaluating the efficacy and safety of gemcitabine plus oxaliplatin in advanced refractory TC is now enrolling patients [19].

Molecular-target therapy

Rationale of molecular-target therapy

In recent years, advances in the genomic knowledge of DTC have opened new therapeutic opportunities.

The MAPK pathway plays a central role in PTC, which is stimulated by activating, and mutually exclusive, mutations in *BRAF* (around 60%), *RAS* family genes (13%) and RET–PTC fusion oncoproteins [20,21]. MAPK activation also promotes expression of other oncoproteins, important for tumor microenvironment [21]. In FTC, *RAS* and *PPARγ* rearrangements are the most-common mutations [21].

Another major signaling pathway is PI3K-AKT-mTOR, which is an important regulator of apoptosis, proliferation and cell migration. Activation of this pathway occurs in FTC, PDTC and ATC and can be the result of gain-of-function mutations in *PI3K* catalytic, alpha polypeptide (PI3KCA) and *AKT1* or inactivating mutations in *PTEN*. Additionally, *RAS* mutations can also stimulate the PI3K-AKT-mTOR pathway, contributing to disease progression in PDTC and ATC, in which cumulative mutations are more frequent [21,22].

Other mutations observed in PDTC and ATC occur in *TP53*, *ALK*, *EGFR*, *TERT* and *EIF1AX-RAS*, the last frequently associated with *RAS* mutations (Figure 1) [22].

Angiogenesis plays a critical role in the proliferation of DTC since peritumoral angiogenesis and microvascular density are increased in aggressive tumors. Higher VEGF and VEGFR, PDGF, and FGF and FGFR tissue levels have also been associated with aggressive behavior [21,23–25].

The expanding knowledge of molecular targets, described in detail in Figure 1, may be clinically relevant. Table 1 exhibits the molecular targets of different clinical relevant inhibitors [26–32].

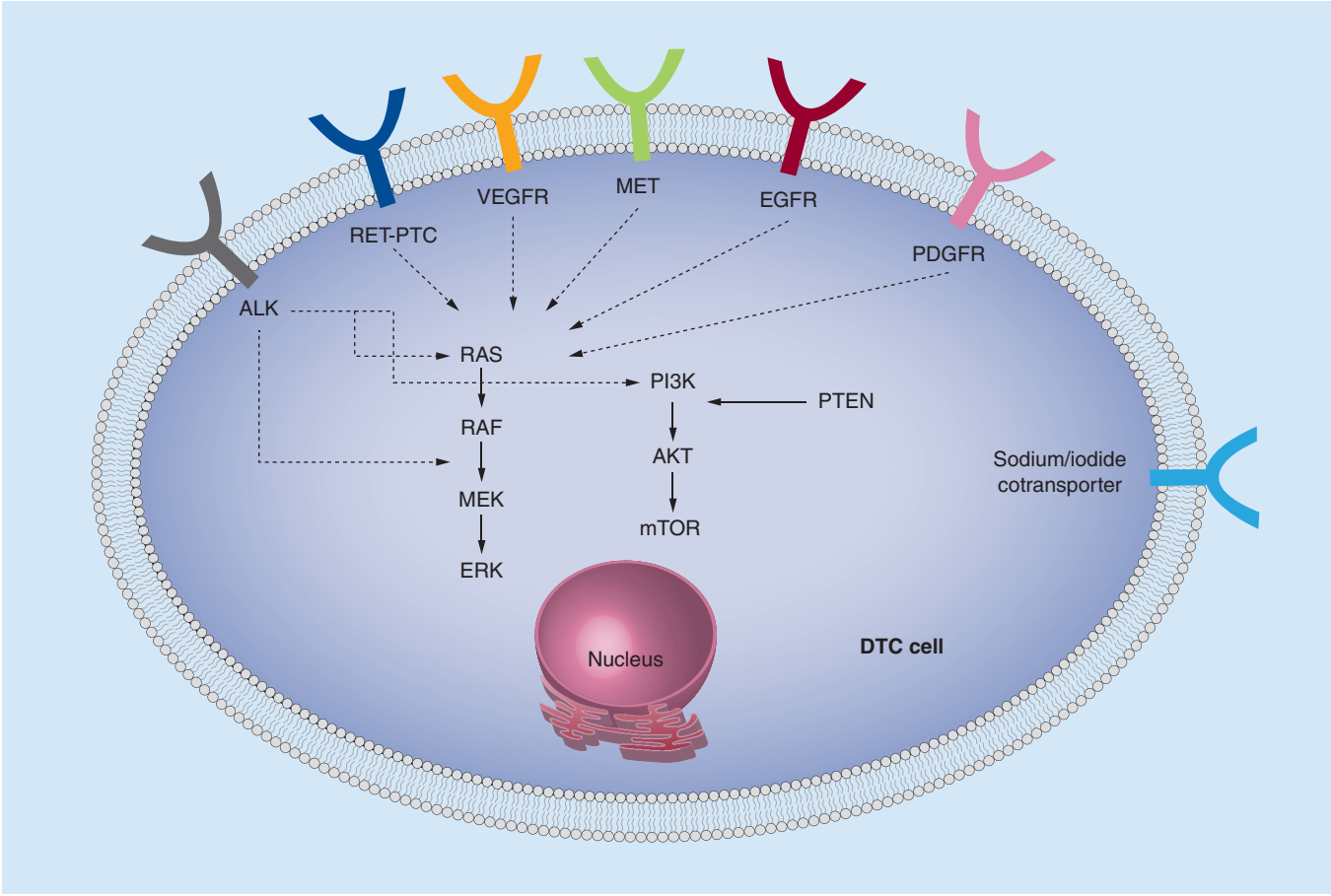

Figure 1. Schematic representation of the major signaling pathways associated with differentiated thyroid cancer.
DTC: Differentiated thyroid cancer; PTC: Papillary thyroid carcinoma.

Efficacy of tyrosine kinase inhibitors in TC

Tyrosine kinase inhibitors (TKIs) are increasingly being used in advanced and RAIRTC, for which the therapeutic options have been limited for decades.

Two TKIs are currently approved for advanced TC, others being used off-label based on the results of Phase II trials [27,29] and some are being studied in Phase I, II or III [27,33–34].

A large systematic review and meta-analysis involving 22 studies and 1435 patients (mostly Phase II trials evaluating response in DTC but also in MTC patients), comprehending ten different TKIs, showed an objective response in 16% of DTC patients. Clinical benefit was observed in 51% of patients. Gefitinib and imatinib induced no objective responses, and pazopanib showed the highest objective response rate in DTC patients (49%). Sorafenib was the most studied TKI showing a clinical benefit in 53% of DTC patients. Lenvatinib studies were not available in this meta-analysis [35].

The DECISION trial was a multicentric, randomized, double-blind, placebo-controlled, Phase III study that investigated sorafenib in patients with locally advanced/metastatic RAIRTC showing recent progression. A total of 417 patients were randomized to sorafenib or placebo (1:1). Approximately 10% of patients had PDTC and 96% of patients had distant metastases. Less than 5% of patients had previously received systemic anticancer therapy [36].

Sorafenib significantly improved progression-free survival (PFS) compared with placebo (median: 10.8 vs 5.8 months, respectively). There was no significant difference in overall survival (OS). Response rates (all partial responses) significantly increased in the sorafenib group compared with placebo (12.2 vs 0.5%). Treatment benefit occurred mostly in patients with lung metastases. Bone metastases showed only modest responses. Biochemical responses were also observed in the sorafenib arm, with initial decreases in serum thyroglobulin levels in most patients.

Table 1. Molecular targets of different clinically relevant inhibitors.

Drug	VEGFR	c-KIT	RET	PDGFR	FGFR	EGFR	Others
Sorafenib	X	X	X	X (β)			RAF, FLT3
Lenvatinib	X	X	X	X (α)	X		KIF5B-RET, CCDC6-RET, NcoA4-RET rearrangement
Sunitinib	X	X	X	X			FLT3
Gefitinib						X	
Imatinib		X		X			Bcr-Abl
Pazopanib	X	X		X			
Vandetanib	X	X	X				
Crizotinib							MET, ALK, ROS1
Lapatinib						X	HER2/3
Cabozantinib	X	X	X				MET, KIF5B-RET rearrangement
Nintendanib	X			X	X		
Tipifarnib							HRAS
Motesanib	X	X	X	X			
Axitinib	X	X		X			
Vemurafenib							BRAF
Dabrafenib							BRAF
Selumetinib							MEK1/2, RAS
Trametinib							MEK1/2
Everolimus							mTOR, PI3K
Temsirolimus							mTOR, PI3K

The SELECT trial was also a Phase III, double-blind study involving patients with progressive RAIRTC, that randomly assigned 261 patients to receive lenvatinib and 131 patients to placebo. Both groups included patients with PDTC, representing more than 10% of the cases. Bone or lung metastases were present in nearly 40 and 90%, respectively, and almost 25% of patients had previously received therapy with TKI [37].

The median PFS was significantly increased in the treatment group: 18.3 months in the lenvatinib group versus 3.6 months with placebo. The response rate was significantly greater in the lenvatinib group (64.8%, including four complete responses) against 1.5% with placebo. Progressive disease occurred in 6.9% of the patients in the lenvatinib group as compared with 39.7% in the placebo group. The difference in OS between groups was not significant.

A subanalysis of the SELECT trial showed a significant benefit in OS in older patients, but this group also had an increased frequency of severe adverse events (AEs) [38].

A PFS benefit associated with lenvatinib and sorafenib was observed in all prespecified subgroups, and within any biomarker/genetic subgroups [36,37].

The benefit of TKI in OS is yet to be proven, will require more extensive trials and may be difficult to prove in crossover-designed trials.

AEs & toxicities

In the DECISION trial, AEs and dose reductions/interruptions due to treatment-related AEs were extremely frequent. The most-common AEs with sorafenib were hand–foot skin reaction, diarrhea, alopecia, rash/desquamation, fatigue, weight loss and hypertension [36].

In the SELECT trial, AEs of any grade occurred in more than 40% of patients in the lenvatinib group, causing drug discontinuation in 14.2 and 2.3% of patients in the active treatment and placebo groups, respectively. Six of the 20 deaths that occurred during the treatment period were considered to be drug related. The main AEs with lenvatinib were hypertension, proteinuria, arterial and venous thromboembolic events, renal and hepatic failure, gastrointestinal fistula, QT prolongation and posterior reversible encephalopathy syndrome [37].

In the meta-analysis of Klein Hesselink *et al.* [35], AEs and dose reductions or discontinuations due to treatment-related AEs were also very common. Sorafenib and cabozantinib were associated with the highest percentage of

Table 2. Most-common adverse events with tyrosine kinase inhibitors and its management.

Toxicity	Comment	Management
General symptoms: including fatigue and weight loss	May be due to AMPK inhibition	Appropriate physical effort adjustment and nutritional support
– Cardiovascular toxicity: HBP/worsening of pre-existing HBP ischemic events, heart failure, QT prolongation – Lesions encasing important blood vessels carry increased hemorrhagic risk	– Cardiovascular toxicity is mainly driven by VEGFR inhibition – Appropriate cardiovascular evaluation before TKI initiation, including arterial pressure, electrocardiogram and echocardiogram in selected patient	– Aggressive treatment of HBP (dihydropyridines may be more effective) – Hold therapy if QTc > 480 ms – Consider delay TKI if recent major cardiovascular event – Avoid TKI in TC lesions encasing important blood vessels
Endocrine effects: increased requirements in levothyroxine (hypothyroidism), calcium and D vitamin (25-hydroxyvitamin D)		– Frequent monitoring of TSH, thyroid hormones and calcium – Appropriate therapy adjustments
Cutaneous effects: HFSR, alopecia, rash, acne, pruritus, dry skin, paronychia, mucositis, yellow skin discoloration	– Most cutaneous AEs result from inhibition of EGFR activity – Yellow skin discoloration is potentially a result of the orange excipient used in sunitinib tablets, a direct effect of the drug or its metabolites	– Avoidance of sun exposure or use SPF 30 UVA/UVB nonocclusive sunscreen – Avoidance of extreme temperatures, physical trauma-like friction and potential irritating agents – Use of ointments, emollients, soap substitutes, urea cream, topical corticosteroids, antihistamines and clindamycin lotion for skin problems – Mouth wash with saline or bicarbonate solutions, antifungals/antibiotics as needed for mucositis
Gastrointestinal effects: diarrhea, nausea/vomiting, aerodigestive fistula, toxic, hepatitis, pancreatitis	– Diarrhea results from EGFR inhibition – Recent digestive surgery, diverticulitis, inflammatory bowel disease or active ulcer increases risk of bleeding or perforation	– Ingestion of isotonic fluids, loperamide and codeine for diarrhea – Frequent monitoring of hepatic blood tests and lipase
Hematological toxicities: bone marrow aplasia		Serial complete blood count
Miscellaneous effects: proteinuria, delayed scarring	– Proteinuria is frequent with lenvatinib – Lenvatinib causes inhibition of FGFR and may significantly delay/impair tissue repair	TKI should be withheld during radiotherapy because of increased risk of local tissue necrosis, major surgery and immediate postoperative period, to allow tissue repair

AE: Adverse event; HBP: High blood pressure; HFSR: Hand–foot skin reaction; SPF: Sun protection factor; TKI: Tyrosine kinase inhibitor; TSH: Thyrotropin-stimulating hormone.

dose reductions or discontinuation (70 and 77%, respectively) due to AEs. The most frequent AEs were hand–foot skin reaction, diarrhea and nausea/vomiting, which could be quite disabling [35].

TKIs can induce multiple AEs that require close monitoring and frequently dosage reductions or therapy suspension, depending on severity. Patients should be instructed about potential AEs and protective measures that can prevent or minimize their severity. The assessment of AEs should comprehend severity scales like the common terminology criteria for AEs since this may help to assist in treatment reductions/withdrawals [39]. Table 2 describes the most common AEs and strategies to manage them [11,40–45].

Timing to stop or switch TKI

Development of severe/intolerable AEs is an obvious reason to stop TKI. Progressive disease under TKI therapy (using the response evaluation criteria in solid tumors criteria) is another logical reason to stop this medication, but we need to bear in mind that there are only a few options for advanced DTC and that progression of disease may accelerate after stopping these agents. There is really no limit on the duration of treatment and some patients will experience years of drug exposure. Whether there is a real benefit of switching from one TKI to another is not clear, nevertheless, this strategy was evaluated in the SELECT trial with favorable results of lenvatinib as a second-line TKI [37]. A retrospective study also analyzed the use of a second-line TKI in advanced TC after first-line TKI failure. TC patients treated with second-line therapy in this study had a stable disease as best response. There were no significant differences in median PFS comparing first- and second-line TKI treatment [45].

Conclusion

We are living in an era of rapid expansion in available therapies for advanced TC. TKIs can provide significant increases in PFS but carry the risk of significant toxicity. Emerging classes in experimental stages will potentially optimize the treatment of TC patients. Redifferentiation of tumors holds great promise for the future. Molecular-

target therapy following a more individualized approach is a matter of special interest. Important steps to achieve efficient, well-tolerated drugs are underway, but significant work still needs to be done.

Future perspective

There are 48 Phase II–IV clinical trials enrolled at clinicaltrials.gov and 22 Phase II–IV at EU Clinical Trials Register. Details about the name of the drugs, phase of the study, primary outcomes, patients enrolled, time of start and estimated time of completion may be seen in Tables 3 & 4 [27,46–47].

BRAF inhibitors

Vemurafenib and dabrafenib are small inhibitors highly selective to the *BRAF-V600E* mutations, which are being studied in Phase II trials [27–30].

Vemurafenib was efficient in some *BRAFV600E*-positive advanced RAIRTC patients (partial responses of 35–38.5% in naive patients and 26–29% in those previously exposed to a VEGFR inhibitor) [29–30,48–49]. Severe AEs were noted in 65 and 68% of the two groups, respectively, [29,48] with 22% developing cutaneous squamous cell carcinoma [28,30].

Dabrafenib revealed positive results in studies with *BRAFV600E*-mutated PTC patients, achieving new RAI uptake and partial and prolonged responses. Dabrafenib was well tolerated, with no patient requiring dose reduction even in long-term treatment [28–29,50–51].

Combination therapy of dabrafenib with lapatinib showed favorable results in patients refractory to other treatments. Dabrafenib associated with trametinib revealed promising results in recurrent TC [27,28]. The most common AEs with these drugs are dermatological, gastrointestinal and constitutional [28,30].

MEK inhibitors

Selumetinib proved to be capable of reintroducing RAI uptake into RAIRTC [29,52]. Despite a disappointing antitumor effect in one study, it was responsible for increasing RAI uptake in 60% of the cases in a mixed group of PTC and PDTC [29]. There seems to be a tumor genotype correlation with changes in RAI avidity, being the *NRAS*-mutant tumors those which benefit the most [29,53–54]. At the present time, monotherapy with selumetinib has achieved only modest success [28,51].

Trametinib is under evaluation in a Phase II study to test tumoral iodine reincorporation in advanced TC [27].

mTOR inhibitors

mTOR upregulation has been associated with TC [55]. Two mTOR inhibitors are being studied, everolimus and temsirolimus. The clinical results with everolimus monotherapy were disappointing, probably due to an early adaptive resistance. This could be related to a feedback loop between mTOR pathway and RAS/MAPK/ERK signaling, resulting in activation of an alternative prosurvival pathway upon mTOR inhibition. Therefore, the use of everolimus in combined therapies is now being studied [28–29,49,55].

The association of sorafenib plus everolimus was already evaluated in a Phase II trial of patients who progressed on sorafenib, showing promising results. This combination is already being used as second-line therapy in centers where lenvatinib is not available [28,49].

ALK inhibitors

ALK gene fusions, involving mainly the striatin gene (*SRTN*), result in increased MAPK activity and have been reported in patients with RAIRTC, specially PDTC and ATC. Crizotinib, a specific inhibitor of *ALK* translocation, showed promising results in *ALK*-mutated TC cell cultures and a clinical trial is currently underway [56,57].

Immunotherapy

Immunotherapy has emerged as a promising therapy since it already proved to be effective in other aggressive tumors. There is evidence of some immunological differences in advanced TC compared with normal thyroidal tissue/nonaggressive TC, such as an overexpression of mast cells, reduced peripheral natural killer cell cytotoxicity, preference by M2 phenotype in tumor-associated macrophages, inefficient dendritic cell maturation, higher concentration of myeloid-derived suppressor cells, T-cell dysfunction and overexpression of regulatory T cells [58,59]. All of this may lead to an immune evasion by cancer cells and progression of the disease [58,59]. There are preclinical and clinical trials at the moment studying therapies targeting tumor-associated macrophages, tumor antigens, T

Table 3. Details about Phase II–IV clinical trials enrolled at clinicaltrials.com which include advanced differentiated thyroid cancer.

Drug	Identifier	Phase of study	Primary outcomes	Patients	Time of start	Estimated time of completion
Anlotinib	NCT02586337	II and III	PFS	RAIRTC	July 2015	December 2017
Apatinib	NCT03048877	III	PFS	Locally advanced or metastatic RAIRTC showing disease progression within 12 months before inclusion	December 2016	December 2019
Lenvatinib	NCT02966093	III	PFS	RAIRTC not eligible for possible curative surgery with evidence of progression within 12 months after initiation of study	February 2017	April 2020
Alectinib	NCT03131206	II	Maximum tolerated dose; ORR	Metastatic RAIRTC that carries an RET rearrangement or an activating RET mutation with disease progression after at least one prior line of systemic therapy	June 2017	May 2020
Apatinib	NCT02731352	II	Disease control rate and ORR	Locally advanced or metastatic RAIRTC showing disease progression within 14 months before inclusion	February 2016	Not mentioned
Apatinib	NCT03167385	II	Disease control rate	Locally advanced or metastatic DTC, which cannot be resected completely, is not suitable or is refractory to RAI with imagiological progression in the last 18 months	March 2017	December 2020
Apatinib	NCT03199677	II	ORR	RAIRTC	July 2017	June 2018
Buparlisib	NCT01830504	II	PFS	Metastatic or locally invasive RAIRTC or PDTC with evidence of progression within the last 12 months	April 2013	January 2017
Cabozantinib	NCT02041260	II	Number of AEs	Metastatic/unresectable RAIRTC with evidence of progression within 14 months before starting treatment	January 2014	January 2018
Cabozantinib	NCT01811212	II	ORR	RAIRTC that has progressed with at least two VEGFR-targeted therapy	May 2013	Not mentioned
CUDC-907	NCT03002623	II	Changes in tumor size and metastases	TC that is refractory to or relapsed after standard treatment	December 2016	March 2025
Cyclophosphamide plus sirolimus	NCT03099356	II	Percentage of patients that respond to treatment	RAIRTC not amenable to curative treatment or who refuse standard treatment	April 2017	May 2023
Dabrafenib, dabrafenib plus trametinib	NCT01723202	II	ORR	RAIRTC or PDTC BRAF mutated with evidence of progression within 13 months before starting the study	November 2012	December 2019
Donafenib	NCT02870569	II	OS	Advanced or metastatic RAIRTC with evidence of disease progression within 14 months prior to initiation of study	September 2016	December 2019
Entrectinib	NCT02568267	II	ORR	Locally advanced or metastatic TC that harbors an NTRK1/2/3, ROS1 or ALK gene rearrangement	October 2015	October 2018
Everolimus plus sorafenib	NCT01263951	II	PFS, ORR and stable disease	Advanced DTC for whom standard curative or palliative measures do not exist or are no longer effective and who have progressed on sorafenib alone	November 2010	Not mentioned
Everolimus	NCT00936858	II	PFS	Advanced or metastatic DTC with evidence of progression by modified RECIST within 6 months before study day 1 and not amenable to or refractory to surgical resection, RT, RAI or other local therapies	July 2009	December 2017
Everolimus, pasireotide, everolimus plus pasireotide	NCT01270321	II	ORR	RAIRTC with evidence of biochemical or radiological progression within the last 12 months prior to enrollment	November 2010	June 2018
Everolimus plus sorafenib	NCT01141309	II	ORR	Progressive surgically inoperable and/or recurrent/metastatic TC with at least one FDG-avid lesion that has not been removed surgically or radiated	June 2010	June 2018

99mTc HMDP: Technetium-99 hydroxymethylene diphosphonate; AE: Adverse event; CT: Computed tomography; DTC: Differentiated thyroid cancer; EAY131: National Cancer Institute (NCI)-Molecular Analysis for Therapy Choice (MATCH); FDG: 8F-fluorodeoxyglucose; FTC: Follicular thyroid cancer; I-124: Iodine-124; IMRT: Intensity-modulated radiation therapy; MTC: Medullary thyroid cancer; NCI-MATCH: Molecularly matched therapy and have no further molecularly matched treatment recommendations per EAY131; ORR: Overall response rate; OS: Overall survival; PERCIST: Positron emission tomography response criteria in solid tumor; PDTC: Poorly differentiated thyroid cancer; PFS: Progression-free survival; RAI: Radioiodine; RAIRTC: Radioiodine refractory thyroid cancer; RECIST: Response evaluation criteria in solid tumor; RT: External beam radiation; TA: Total activity; TC: Thyroid cancer.

Table 3. Details about Phase II–IV clinical trials enrolled at clinicaltrials.com which include advanced differentiated thyroid cancer (cont.).

Drug	Identifier	Phase of study	Primary outcomes	Patients	Time of start	Estimated time of completion
Gemcitabine plus oxaliplatin	NCT02472080	II	ORR (complete and partial responses) measured by CT scan according to RECIST criteria	Metastatic or unresectable RAIRTC or PDTC with radiologic evidence of clinically relevant disease progression	April 2016	July 2018
IMRT plus doxorubicin	NCT01882816	II	Rates of local/regional PFS	Nonanaplastic non-MTC that is either grossly recurrent after surgery or unresectable with or without metastatic disease	June 2013	June 2018
Ipilimumab plus nivolumab	NCT02834013	II	ORR	Rare cancer that does not have a match to a molecularly guided therapy on EAY131 protocol or who progressed on NCI-MATCH and there are no other approved/standard therapies available that have shown to prolong OS	January 2017	Not mentioned
Larotrectinib	NCT02576431	II	ORR	Locally advanced or metastatic TC with an NTRK1/2/3 gene fusion that have received or are unlikely to tolerate/benefit standard therapy	October 2015	December 2019
Lenalidomida	NCT00287287	II	Tumor response	Unresectable, distantly metastatic RAIRTC with imagiological progression within the last 12 months	February 2006	December 2017
Lenvatinib	NCT02702388	II	Evaluate whether an oral starting dose of 18-mg daily will provide comparable efficacy to a 24 mg starting dose, but a better safety profile	RAIRTC with disease progression within 12 months	March 2016	October 2020
Lenvatinib plus everolimus	NCT03139747	II	Number of subjects with PFS	Metastatic or unresectable DTC for which standard curative or palliative measures do not exist or are no longer effective that have progressed on lenvatinib alone (but with previous stable disease for at least 4 months)	April 2017	April 2020
Nintendanib	NCT01788982	II	PFS	Locally advanced or metastatic DTC deemed incurable by surgery, radiotherapy and/or RAI	May 2014	January 2018
Nivolumab plus ipilimumab	NCT03246958	II	Radiographic response rate	Metastatic RAIRTC with progression within 13 months prior to study registration	September 2017	March 2025
Pazopanib	NCT01813136	II	Time to treatment failure comparing continuous with intermittent schedule	RAIRTC or PDTC with imagiological evidence of progression within the last 12 months	March 2013	June 2018
Pazopanib	NCT00625846	II	Confirmed tumor response; proportion of patients who have achieved an objective response	Advanced or metastatic RAIRTC, MTC or ATC with evidence of disease progression within 6 months before starting treatment	February 2008	Not mentioned
Pembrolizumab and lenvatinib	NCT02973997	II	Confirmed response rate	Locally recurrent and unresectable and/or distant metastatic RAIRTC with evidence of progression within 14 months or progression with lenvatinib alone within 30 days before starting the study	April 2017	Not mentioned
Pembrolizumab	NCT02628067	II	ORR	Progressive TC intolerant to therapies known to provide clinical benefit	December 2015	August 2023
Radium 223	NCT02390934	II	Metabolic response according to PERCIST criteria	RAIRTC with at least one bone metastasis observed on CT/MRI, with uptake on PET-FDG and 99mTc-HMDP bone scintigraphy or FNa PET/CT	October 2014	March 2018
Selumetinib plus RAI	NCT02393690	II	Response rate	Recurrent and/or metastatic TC with a RAI-avid lesion on an RAI scan performed within 24 months before therapy	May 2015	August 2020
Sorafenib, sorafenib plus everolimus	NCT02143726	II	PFS	Metastatic or locally advanced unresectable refractory Hurthle cell TC with evidence of progression on the 14 months before study whom are naive for sorafenib and mTOR inhibitor	October 2014	Not mentioned

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Table 3. Details about Phase II–IV clinical trials enrolled at clinicaltrials.com which include advanced differentiated thyroid cancer (cont.).

Drug	Identifier	Phase of study	Primary outcomes	Patients	Time of start	Estimated time of completion
Sorafenib	NCT02084732	II	Describe the clinical activity and safety profile	Metastatic or unresectable DTC for whom conventional curative or palliative therapeutic options do not exist or are not effective	October 2013	June 2018
Sulfatinib	NCT02614495	II	ORR	Locally advanced and/or metastatic RAIRTC or MTC with evidence of disease progression within 12 months before starting therapy	February 2016	December 2018
Temsirolimus plus sorafenib	NCT01025453	II	ORR	Progressive surgically inoperable and/or recurrent/metastatic RAIRTC with at least one FDG-avid lesion that has not been removed surgically or radiated	December 2009	December 2017
Trametinib plus RAI, trametinib plus dabrafenib plus RAI	NCT03244956	II	ORR	RAIRTC (TA ≤300 mCi) positive for RAS mutation with progression of disease within 18 months prior initiation of therapy and absence of metastatic lesion >30 mm	July 2017	August 2022
Trametinib	NCT02152995	II	Iodine incorporation in TC metastases to a predicted lesional absorbed radiation dose ≥2000 cGy with the administration of ≤300 mCi RAI; ORR; PFS; proportion of patients alive following treatment with trametinib and I-124	RAIRTC	August 2014	Not mentioned
Tipifarnib	NCT02383927	II	ORR	Relapsed or refractory to prior therapy TC with missense HRAS mutation	March 2015	December 2017
Vemurafenib	NCT01709292	II	Percent change in ERK phosphorylation and tumor size. Evaluate the existence of correlation between these two variables	Locally advanced DTC requiring surgical treatment	November 2012	November 2019
Avelumab plus checkpoint agonist(s) with or without RT or RT plus cisplatin	NCT03217747	I/II	AEs	Advanced TC refractory or intolerant to established therapy known to provide clinical benefit, or where subjects refuse existing therapies	August 2017	August 2022
Cediranib maleate with or without lenalidomide	NCT01208051	I/II	Maximum-tolerated dose (Phase I); PFS (Phase II)	RAIRTC with evidence of disease progression within the last 12 months	September 2010	September 2017
HuMax-AXL-ADC	NCT02988817	I/II	Dose limiting toxicities; AEs	Relapsed, advanced or metastatic TC who have failed available standard therapy or who are not candidates for standard therapy	December 2016	June 2021
Lenvatinib	NCT02432274	I/II	ORR	RAIRTC	December 2014	September 2018
LOXO-195	NCT03215511	I/II	Maximum-tolerated dose (Phase I); recommended dose for further study (Phase I); best ORR (Phase II)	TC with NTRK fusion treated with prior TRK inhibitor or TC do not benefit greatly with other standard or investigational therapies	July 2017	December 2019
Sacituzumab govitecan	NCT01631552	I/II	Safety	Metastatic FTC refractory to or relapsed after at least one prior standard therapeutic regimen	February 2013	June 2018

99mTc HMDP: Technetium-99 hydroxymethylene diphosphonate; AE: Adverse event; CT: Computed tomography; DTC: Differentiated thyroid cancer; EAY131: National Cancer Institute (NCI)-Molecular Analysis for Therapy Choice (MATCH); FDG: 8F-fluorodeoxyglucose; FTC: Follicular thyroid cancer; I-124: Iodine-124; IMRT: Intensity-modulated radiation therapy; MTC: Medullary thyroid cancer; NCI-MATCH: Molecularly matched therapy and have no further molecularly matched treatment recommendations per EAY131; ORR: Overall response rate; OS: Overall survival; PERCIST: Positron emission tomography response criteria in solid tumor; PDTC: Poorly differentiated thyroid cancer; PFS: Progression-free survival; RAI: Radioiodine; RAIRTC: Radioiodine refractory thyroid cancer; RECIST: Response evaluation criteria in solid tumor; RT: External beam radiation; TA: Total activity; TC: Thyroid cancer.

cells, natural killer cells and immune checkpoints [58–60]. Also, combination therapy of TKIs with other drugs such as immune checkpoint inhibitors is a matter of special interest [61].

Immune checkpoint inhibitors at the moment have the biggest role in this class since they are the novelty responsible for improving outcomes seen in other tumors such as melanoma [62]. A study of pembrolizumab in advanced solid tumors included 22 patients with advanced DTC who failed standard treatment and showed an

Table 4. Details about Phase II–IV clinical trials enrolled at EU Clinical Trials Register which includes advanced differentiated thyroid cancer.

Drug	EudraCT number	Phase of study	Primary outcomes	Patients	Time of start	Estimated time of completion
Lenvatinib	2010-023783-41	III	PFS	RAIRTC with radiographic evidence of disease progression within the prior 12 months	July 2011	Not mentioned
Sorafenib	2009-012007-25	III	PFS	Locally advanced/metastatic RAIRTC or PDTC not candidates for surgery or RT with curative intent and with evidence of progression within 14 months prior to enrollment	October 2009	Not mentioned
Sunitinib	2006-006538-16	III	Continue sunitinib treatment	TC subjects that have participated in a previous parent or extension of sunitinib study and are thought to have the potential to derive clinical benefit from continued treatment	March 2017	Not mentioned
Vandetanib	2013-000422-58	III	PFS	Locally advanced or metastatic RAIRTC/PDTC not amenable to surgical resection, RT or other local therapy	July 2013	Not mentioned
Crizotinib	2013-000885-13	II	ORR	Metastatic or unresectable locally advanced TC with MET mutation considered by the investigator as not amenable to any other validated therapeutic option	July 2013	2019
Dabrafenib plus trametinib	2013-001705-87	II	ORR	Advanced TC BRAF mutated with no available standard treatment options	March 2014	2020
Everolimus	2009-016669-27	II	Efficacy	Irresectable recurrent or metastatic RAIRTC, ATC and MTC with evidence of progression within the 14 months before starting the therapy	April 2010	Not mentioned
Lenvatinib	2007-005933-12	II	ORR	Unresectable RAIRTC or MTC with evidence of disease progression within the last 12 months before starting the study	October 2009	Not mentioned
Lenvatinib	2014-005199-27	II	Determine whether a starting dose of 20 mg or 14 mg QD will provide comparable efficacy with an improved safety profile compared with 24 mg QD	RAIRTC showing progression of disease within 12 months before starting therapy	May 2016	2019
Nivolumab	2016-000461-23	II	Clinical benefit rate	Advanced/metastatic RAIRTC	March 2017	2023
Nintedanib	2012-004295-19	II	PFS	Locally advanced or metastatic DTC/MTC deemed incurable by surgery, RT and/or RAI with evidence of progression within 12 months before starting the study	August 2014	2019
Pembrolizumab	2016-002260-14	II	ORR	Unresectable locally advanced or metastatic DTC, PDTC, MTC or ATC which are resistant or refractory to standard therapy, or for which standard therapy does not exist, or is not considered appropriate, and for which no other experimental treatment options are available	April 2017	2023
Pembrolizumab	2015-002067-41	II	ORR	Metastatic and/or unresectable DTC that is incurable and for which prior standard first-line treatment has failed	January 2016	2023
Selumetinib	2013-000423-14	II	Complete remission rate in the general population and in patients harboring BRAF or NRAS mutation	DTC T3a-T4 or at least 1 lymph node that is ≥1 cm or ≥5 involved lymph nodes (of any size)	May 2013	2017
Selumetinib	2015-002269-47	II	PFS	Locally advanced or metastatic RAIRTC or PDTC	December 2015	2019
Sorafenib	2006-006615-80	II	ORR	Advanced or metastatic DTC or MTC not suitable for RAI	February 2007	Not mentioned
Tipifarnib	2015-004535-12	II	ORR	HRAS mutation TC that has relapsed or is refractory to prior therapy	February 2016	2018
Trametinib plus RAI with/without dabrafenib	2017-000742-21	II	ORR	Metastatic RAIRTC or PDTC with RAS or BRAF mutation showing progression of disease within 18 months before starting the study	July 2017	2022
Vandetanib	2007-001890-27	II	PFS	Advanced or metastatic RAIRTC	June 2007	Not mentioned

ATC: Anaplastic thyroid cancer; DTC: Differentiated thyroid cancer; MTC: Medullary thyroid cancer; ORR: Overall response rate; PDTC: Poorly differentiated thyroid cancer; PFS: Progression-free survival; QD: Once-daily; RAI: Radioiodine; RAIRTC: Radioiodine refractory thyroid cancer; RT: External beam radiation; TC: Thyroid cancer.

Table 4. Details about Phase II–IV clinical trials enrolled at EU Clinical Trials Register which includes advanced differentiated thyroid cancer (cont.).

Drug	EudraCT number	Phase of study	Primary outcomes	Patients	Time of start	Estimated time of completion
Vemurafenib	2014-001225-33	II	Efficacy	Unresectable locally advanced or metastatic TC harboring BRAF mutations refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the investigator and are not eligible to an appropriate ongoing clinical trial	July 2014	2021
AZD2014 plus selumetinib	2014-002613-31	IB/IIA	Establish the feasible dose levels and regimens of AZD2014 and selumetinib when given in combination	Metastatic or locally advanced TC with alteration in ≥1 gene involved in PI3K/AKT/mTOR or Ras/MEK pathway signaling which is not amenable to resection and refractory to conventional treatment or for which no conventional therapy exists	April 2015	2017
WX-554	2011-003408-19	I/II	Determine the optimum biological, the maximum tolerated and the recommended doses/dose schedules (Phase I); determine the safety and tolerability of chronic treatment	Advanced, metastatic and/or progressive TC for whom there is no effective standard therapy available	January 2012	Not mentioned

ATC: Anaplastic thyroid cancer; DTC: Differentiated thyroid cancer; MTC: Medullary thyroid cancer; ORR: Overall response rate; PDTC: Poorly differentiated thyroid cancer; PFS: Progression-free survival; QD: Once-daily; RAI: Radioiodine; RAIRTC: Radioiodine refractory thyroid cancer; RT: External beam radiation; TC: Thyroid cancer.

expression of PD-L1 ≥1% or stroma cell lines by immunohistochemistry. Preliminary results showed a 54.5% rate of stable disease, 9% rate of partial response, a 6-month OS rate of 100% and a 58.7% rate of 6-month PFS. Despite 18 patients had treatment-related AE, none of the patients needed to discontinue the drug [62]. At clinicaltrials.gov and EU Clinical Trials Register there are several studies ongoing with these drugs, such as ipilimumab plus nivolumab (two Phase II studies), pembrolizumab plus lenvatinib (one Phase II study), pembrolizumab alone (three Phase II studies), nivolumab alone (one Phase II study) and avelumab plus checkpoint agonist(s) with or without irradiation or irradiation plus cisplatin (one Phase I/II study). So, in the next few years, we will probably be able to have evidence of the efficacy of these drugs in RAIRTC [46,47].

Microtubule inhibitors

CA4 is a naturally occurring inhibitor of tubulin that acts as an antimitotic agent, causing vascular shutdown and cell death. CA4 has already shown cytotoxic and antiproliferative activity in a variety of cancers. Recently, in a preclinical study using human thyroid papillary carcinoma cell line TPC1, CA4 showed the capacity to inhibit proliferation, migration and invasion and of promoting apoptosis. Due to these results, CA4 is considered a potential therapeutic target for the treatment of TC [63].

Other investigational therapies

New multi-TKIs (pyrazolopyrimidines and derivatives of CLM3) and other therapeutic classes such as inhibitors of aurora kinases, proteasome, kinesin spindle protein, cancer stem cells and histone deacetylases, flavonoids, gene and apoptotic cell death-based therapies have already shown promising results in preclinical studies, and may have a role in advanced TC therapy in the future [26–27,58–60,64–71].

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Executive summary

- The majority of differentiated thyroid cancers have a good prognosis. A minority, however, will become refractory to radioiodine and progress with local recurrence and/or distant metastases.
- Conventional cytotoxic chemotherapy has been largely replaced by molecularly targeted therapies, but it can still be useful in some patients.
- Two tyrosine kinase inhibitors have been approved for the treatment of advanced differentiated thyroid cancer (sorafenib and lenvatinib). They significantly improve progression-free survival, but at the cost of frequent and potentially serious adverse effects and without clear benefit in overall survival.
- Other multitarget tyrosine kinase inhibitors are under investigation at the moment, some with good results in preclinical trials.
- Dabrafenib and selumetinib showed promising results in the redifferentiation of thyroid tumors.
- Association of sorafenib plus everolimus showed favorable results. The association of everolimus with other drugs (i.e., lenvatinib) is being studied.
- Other drug classes such as immune checkpoint inhibitors may also have therapeutic potential.

References

1. American Cancer Society. Cancer facts and figures (2015). www.cancer.org/research/cancer-facts- statistics.html
2. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer* 115(16), 3801–3807 (2009).
3. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer 'epidemic' – screening and overdiagnosis. *N. Engl. J. Med.* 371(19), 1765–1767 (2014).
4. Brito JP, Al Nofal A, Montori VM, Hay ID, Morris JC. The Impact of subclinical disease and mechanism of detection on the rise in thyroid cancer incidence: a population-based study in Olmsted County, Minnesota during 1935 through 2012. *Thyroid* 25(9), 999–1007 (2015).
5. Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. *Nat. Rev. Endocrinol.* 8(8), 466–475 (2012).
6. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clin. Oncol. (R. Coll. Radiol.)*, 22(6), 486–497 (2010).
7. Veiga LH, Neta G, Aschebrook-Kilfoy B, Ron E, Devesa SS. Thyroid cancer incidence patterns in Sao Paulo, Brazil, and the US SEER program, 1997–2008. *Thyroid* 23(6), 748–757 (2013).
8. Surov A, Gottschling S, Wienke A, Meyer HJ, Spielmann RP, Dralle H. Primary thyroid sarcoma: a systematic review. *Anticancer Res.* 35(10), 5185–5191 (2015).
9. Chai YJ, Hong JH, Koo do H *et al.* Clinicopathological characteristics and treatment outcomes of 38 cases of primary thyroid lymphoma: a multicenter study. *Ann. Surg. Treat. Res.* 89(6), 295–299 (2015).
10. Spitzweg C, Bible KC, Hofbauer LC, Morris JC. Advanced radioiodine-refractory differentiated thyroid cancer: the sodium iodide symporter and other emerging therapeutic targets. *Lancet Diabetes Endocrinol.* 2(10), 830–842 (2014).
11. Haugen BR, Alexander EK, Bible KC *et al.* 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 26(1), 1–133 (2016).
12. Durante C, Haddy N, Baudin E *et al.* Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J. Clin. Endocrinol. Metab.* 91(8), 2892–2899 (2006).
13. Schlumberger M, Brose M, Elisei R *et al.* Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes Endocrinol.* 2(5), 356–358 (2014).
14. Albero A, Lopez JE, Torres A, de la Cruz L, Martin T. Effectiveness of chemotherapy in advanced differentiated thyroid cancer: a systematic review. *Endocr. Relat. Cancer* 23(2), R71–R84 (2016).
15. Matuszczyk A, Petersenn S, Bockisch A *et al.* Chemotherapy with doxorubicin in progressive medullary and thyroid carcinoma of the follicular epithelium. *Horm. Metab. Res.* 40(3), 210–213 (2008).
16. Hussein O, Karen D, Zidan J. Cisplatin based chemotherapy in patients with advanced differentiated thyroid carcinoma refractory to I131 treatment. *Indian J. Med. Paediatr. Oncol.* 34(4), 234–237 (2013).

17. Santini F, Bottici V, Elisei R *et al.* Cytotoxic effects of carboplatinum and epirubicin in the setting of an elevated serum thyrotropin for advanced poorly differentiated thyroid cancer. *J. Clin. Endocrinol. Metab.* 87(9), 4160–4165 (2002).
18. Spano JP, Vano Y, Vignot S *et al.* GEMOX regimen in the treatment of metastatic differentiated refractory thyroid carcinoma. *Med. Oncol.* 29(3), 1421–1428 (2012).
19. Paris AP-Hd. Gemcitabine – oxaliplatin for advanced refractory thyroid cancer patients: a Phase II study (THYGEMOX). ClinicalTrials.gov (2016).
20. Integrated genomic characterization of papillary thyroid carcinoma. *Cell* 159(3), 676–690 (2014).
21. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat. Rev. Cancer* 13(3), 184–199 (2013).
22. Landa I, Ibrahimpasic T, Boucai L *et al.* Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J. Clin. Invest.* 126(3), 1052–1066 (2016).
23. Ishiwata T, Iino Y, Takei H, Oyama T, Morishita Y. Tumor angiogenesis as an independent prognostic indicator in human papillary thyroid carcinoma. *Oncol. Rep.* 5(6), 1343–1348 (1998).
24. Klein M, Vignaud JM, Hennequin V *et al.* Increased expression of the vascular endothelial growth factor is a pejorative prognosis marker in papillary thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 86(2), 656–658 (2001).
25. Lennard CM, Patel A, Wilson J *et al.* Intensity of vascular endothelial growth factor expression is associated with increased risk of recurrence and decreased disease-free survival in papillary thyroid cancer. *Surgery* 129(5), 552–558 (2001).
26. Ferrari SM, La Motta C, Sartini S *et al.* Pyrazolopyrimidine derivatives as antineoplastic agents: with a special focus on thyroid cancer. *Mini Rev. Med. Chem.* 16(2), 86–93 (2016).
27. Antonelli A, La Motta C. Novel therapeutic clues in thyroid carcinomas: the role of targeting cancer stem cells. *Med. Res. Rev.* 37(6), 1299–1317 (2017).
28. Bikas A, Vachhani S, Jensen K, Vasko V, Burman KD. Targeted therapies in thyroid cancer: an extensive review of the literature. *Expert Rev. Clin. Pharmacol.* 15, 1–15 (2016).
29. Lirov R, Worden FP, Cohen MS. The treatment of advanced thyroid cancer in the age of novel targeted therapies. *Drugs* 77(7), 733–745 (2017).
30. Cabanillas ME, Patel A, Danysh BP, Dadu R, Kopetz S, Falchook G. BRAF inhibitors: experience in thyroid cancer and general review of toxicity. *Horm. Cancer* 6(1), 21–36 (2015).
31. Viola D, Valerio L, Molinaro E *et al.* Treatment of advanced thyroid cancer with targeted therapies: ten years of experience. *Endocr. Relat. Cancer* 23(4), R185–R205 (2016).
32. Bible KC, Ryder M. Evolving molecularly targeted therapies for advanced-stage thyroid cancers. *Nat. Rev. Clin. Oncol.* 13(7), 403–416 (2016).
33. Carr LL, Mankoff DA, Goulart BH *et al.* Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. *Clin. Cancer Res.* 16(21), 5260–5268 (2010).
34. Bible KC, Suman VJ, Molina JR *et al.* Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a Phase II consortium study. *Lancet Oncol.* 11(10), 962–972 (2010).
35. Klein Hesselink EN, Steenvoorden D, Kapiteijn E *et al.* Therapy of endocrine disease: response and toxicity of small-molecule tyrosine kinase inhibitors in patients with thyroid carcinoma: a systematic review and meta-analysis. *Eur. J. Endocrinol.* 172(5), R215–R225 (2015).
36. Brose MS, Nutting CM, Jarzab B *et al.* Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, Phase III trial. *Lancet* 384(9940), 319–328 (2014).
37. Schlumberger M, Tahara M, Wirth LJ *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* 372(7), 621–630 (2015).
38. Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the Phase III SELECT trial. *J. Clin. Oncol.* 35(23), 2692–2699 (2017).
39. US Department Of Health And Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) (2010). https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
40. Zamorano JL, Lancellotti P, Rodriguez Munoz D *et al.* 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur. Heart J.* 37(36), 2768–2801 (2016).
41. Ancker OV, Wehland M, Bauer J, Infanger M, Grimm D. The adverse effect of hypertension in the treatment of thyroid cancer with multi-kinase inhibitors. *Int. J. Mol. Sci.* 18(3), pii:E625 (2017) (Epub ahead of print).
42. Califano R, Tariq N, Compton S *et al.* Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK. *Drugs* 75(12), 1335–1348 (2015).

43. Aparicio-Gallego G, Blanco M, Figueroa A *et al.* New insights into molecular mechanisms of sunitinib-associated side effects. *Mol. Cancer Ther.* 10(12), 2215–2223 (2011).
44. Aw DC, Tan EH, Chin TM, Lim HL, Lee HY, Soo RA. Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. *Asia Pac. J. Clin. Oncol.* doi:10.1111/ajco.12687 (2017) (Epub ahead of print).
45. Massicotte MH, Brassard M, Claude-Desroches M *et al.* Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: a retrospective study of the TUTHYREF network. *Eur. J. Endocrinol.* 170(4), 575–582 (2014).
46. EU Clinical Trials Register (2017). www.clinicaltrialsregister.eu/
47. ClinicalTrials (2017). https://clinicaltrials.gov/
48. Brose MS, Cabanillas ME, Cohen EE *et al.* Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, Phase II trial. *Lancet Oncol.* 17(9), 1272–1282 (2016).
49. Brose MS. Sequencing of tyrosine kinase inhibitors in progressive differentiated thyroid cancer. *Clin. Adv. Hematol. Oncol.* 14(Suppl. 9), 7–12 (2016).
50. Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. *Clin. Cancer Res.* 21(5), 1028–1035 (2015).
51. Falchook GS, Millward M, Hong D *et al.* BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. *Thyroid* 25(1), 71–77 (2015).
52. Chow LQ, Santana-Davila R, Pantel A *et al.* A Phase I study of pazopanib in combination with escalating doses of 131I in patients with well-differentiated thyroid carcinoma borderline refractory to radioiodine. *PLoS ONE* 12(6), e0178325 (2017).
53. AstraZeneca. Study comparing complete remission after treatment with selumetinib/placebo in patient with differentiated thyroid cancer (ASTRA). ClinicalTrials.gov Identifier: NCT01843062 (2017). https://clinicaltrials.gov/ct2/show/NCT01843062
54. United AaCCR. Iodine I-131 with or without selumetinib in treating patients with recurrent or metastatic thyroid cancer. ClinicalTrials.gov Identifier: NCT02393690 (2017). https://clinicaltrials.gov/ct2/show/NCT02393690
55. Schneider TC, de Wit D, Links TP *et al.* Everolimus in patients with advanced follicular-derived thyroid cancer: results of a Phase II clinical trial. *J. Clin. Endocrinol. Metab.* 102(2), 698–707 (2017).
56. Kelly LM, Barila G, Liu P *et al.* Identification of the transforming STRN–ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. *Proc. Natl Acad. Sci. USA* 111(11), 4233–4238 (2014).
57. Zhou Y, Zhao C, Gery S *et al.* Off-target effects of c-MET inhibitors on thyroid cancer cells. *Mol. Cancer Ther.* 13(1), 134–143 (2014).
58. Bastman JJ, Serracino HS, Zhu Y *et al.* Tumor-infiltrating T cells and the PD-1 checkpoint pathway in advanced differentiated and anaplastic thyroid cancer. *J. Clin. Endocrinol. Metab.* 101(7), 2863–2873 (2016).
59. French JD, Bible K, Spitzweg C, Haugen BR, Ryder M. Leveraging the immune system to treat advanced thyroid cancers. *Lancet Diabetes Endocrinol.* 5(6), 469–481 (2017).
60. Parhar RS, Zou M, Al-Mohanna FA *et al.* IL-12 immunotherapy of Braf(V600E)-induced papillary thyroid cancer in a mouse model. *Lab. Invest.* 96(1), 89–97 (2016).
61. Ito Y, Suzuki S, Ito K *et al.* Tyrosine-kinase inhibitors to treat radioiodine-refracted, metastatic, or recurred and progressive differentiated thyroid carcinoma. *Endocr. J.* 63(7), 597–602 (2016).
62. Cunha LL, Marcello MA, Rocha-Santos V, Ward LS. Immunotherapy against endocrine malignancies: immune checkpoint inhibitors lead the way. *Endocr. Relat. Cancer* pii:ERC-17-0222 (2017) (Epub ahead of print).
63. Liang W, Lai Y, Zhu M, Huang S, Feng W, Gu X. Combretastatin A4 regulates proliferation, migration, invasion, and apoptosis of thyroid cancer cells via PI3K/Akt signaling pathway. *Med. Sci. Monit.* 22, 4911–4917 (2016).
64. Baldini E, Tuccilli C, Prinzi N *et al.* Selective inhibitors of aurora kinases inhibit proliferation, reduce cell viability and impair cell cycle progression in papillary thyroid carcinoma cells. *J. Biol. Regul. Homeost. Agent* 29(4), 793–803 (2015).
65. Quagliariello V, Armenia E, Aurilio C *et al.* New treatment of medullary and papillary human thyroid cancer: biological effects of hyaluronic acid hydrogel loaded with quercetin alone or in combination to an inhibitor of aurora kinase. *J. Cell. Physiol.* 231(8), 1784–1795 (2016).
66. Sui GQ, Fei D, Guo F *et al.* MicroRNA-338–3p inhibits thyroid cancer progression through targeting AKT3. *Am. J. Cancer Res.* 7(5), 1177–1187 (2017).
67. Celano M, Mio C, Sponziello M *et al.* Targeting post-translational histone modifications for the treatment of non-medullary thyroid cancer. *Mol. Cell. Endocrinol.* pii:S0303-7207(17)30305-2 (2017) (Epub ahead of print).
68. Broecker-Preuss M, Becher-Boveleth N, Muller S, Mann K. The BH3 mimetic drug ABT-737 induces apoptosis and acts synergistically with chemotherapeutic drugs in thyroid carcinoma cells. *Cancer Cell Int.* 16, 27 (2016).
69. Hussain AR, Bu R, Ahmed M *et al.* Role of X-linked inhibitor of apoptosis as a prognostic marker and therapeutic target in papillary thyroid carcinoma. *J. Clin. Endocrinol. Metab.* 100(7), E974–E985 (2015).

70. Infante JR, Patnaik A, Verschraegen CF *et al.* Two Phase I dose-escalation studies exploring multiple regimens of litronesib (LY2523355), an Eg5 inhibitor, in patients with advanced cancer. *Cancer Chemother. Pharmacol.* 79(2), 315–326 (2017).

71. Mutlu Altundag E, Kasaci T, Yilmaz AM *et al.* Quercetin-induced cell death in human papillary thyroid cancer (B-CPAP) cells. *J. Thyroid Res.* 2016, 9843675 (2016).